UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,853	01/26/2004	Antony Bigot	ST01033 US CNT	9800

5487 7590 12/17/2004

ROSS J. OEHLER
AVENTIS PHARMACEUTICALS INC.
ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
PAVIGLIANITI, ANTHONY JOSEPH	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,853	BIGOT ET AL.	
	Examiner	Art Unit	
	Anthony J. Paviglianiti	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) 1 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-8 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/291,084.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 – 8 are currently pending in the instant application and are subject to the following restriction. Claim 1 was withdrawn. Claims 2 – 8 were examined and are rejected.

Priority

This application is a Continuation of parent Application No. 10/291,084, filed on November 8, 2002, now U.S. Patent No. 6,699,867, issued March 2, 2004.

This application further claims priority to Provisional Application No. 60/352,797, filed on January 30, 2002.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy of French patent application FR 0114510 (filing date November 9, 2001) has been filed in parent Application No. 10/291,084 (filing date November 8, 2002).

Election/Restrictions

Restriction to one of the following Groups is required under 35 U.S.C. §121:

I. Claim 1, drawn to a process of preparing a compound of Formula (II), which is unable to be classified without providing definitions for X and Y in Claim 1.

II. Claims 2 – 8, drawn to methods of treating an illness by administering a compound of Formula (I) to a patient, classified in class 514, in various subclasses.

In addition to an election of one of the above Groups, restriction is further required under 35 U.S.C. §121 as follows:

If **Group I** is elected, then election of a single compound is required, where an exact definition of X and Y in the heterocyclic ring of Formula (II) must be made.

If **Group II** is elected, then election of a specific method of use *and an elected compound of Formula (I)* is required.

As to election of a specific method of use, an example from the following list could be selected:

A. Method of treating Parkinson's Disease; or

B. Method of treating Huntington's Disease; or

C. Method of treating Alzheimer's Disease; or

D. Method of treating Multiple Sclerosis; or

E. Method of treating Amyotrophic Lateral Sclerosis; or

F. Method of treating migraine; or

G. Method of treating depression; or

H. Method of treating schizophrenia; or

I. Method of treating anxiety; or

J. Method of treating epilepsy.

In accordance with the decisions in In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980) and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App & Int. 1984), restriction of a Markush group is proper where the compounds with the group either (1) do not share a common utility, or (2) do not share a substantial structural feature disclosed as being essential to that utility. In addition, a Markush group may encompass a plurality of independent and distinct inventions where two or more members are so unrelated and diverse that a prior art reference

anticipating the claim with respect to one of the members would not render the claim obvious under 35 U.S.C. §103 with respect to the other member(s).

If one of the methods of treatment of **Group II** is elected, **an election of a single compound of Formula (I) to be used is further required**, including an exact definition of each substitution on the base molecule [Formula (I)], where a single member at each substituent group is selected. For example, if the base molecule has ring elements **X** and **Y**, where **X** is recited to be any one of the following: O, NH, N-(C_1-C_4) alkyl, N-benzyl, N-phenyl, N-(2-pyridyl), N-2-pyrimidyl, S, SO, SO_2, CH_2 and CH-phenyl, and **Y** is either $-CH_2-$ or C=O, then applicant must select a single value for **X**, such as Oxygen, and a single value for **Y**, such as CH_2.

One suggestion for the election of a compound would be to select one from the list of compounds described in Claim 3 or Claim 4, or to select one of the compounds disclosed in the Specification.

In the instant case, upon election of a single compound and method of use, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound and disease (compounds and diseases which are so similar as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim which fall into the same class and subclass as the elected compound and disease, but may also include additional compounds which fall in related subclasses.

Examination will then proceed on the elected compound and disease *and* the entire scope of the invention encompassing the elected compound as defined by common classification. A

clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits.

Note that the restriction requirement will not be made final until such time as Applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making the compounds under investigation. This will be set forth by reference to specific class(es) and subclass(es) examined.

Should Applicant traverse on the ground that the compounds are not patentably distinct, Applicant should submit evidence or identify such evidence now of record showing the compounds or diseases to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. §103(a) of the other invention.

All compounds and diseases falling outside of the class(es) and subclass(es) of the selected compound and any other subclass encompassed by the election above will be directed to non-elected subject matter and will be withdrawn from consideration under 35 U.S.C. §121 and 37 C.F.R. §1.142(b). Applicant may reserve the right to file divisional applications on the remaining subject matter. The provisions of 35 U.S.C. §121 apply with regard to double patenting covering divisional applications.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(i).

If desired upon election of a single compound and disease state, applicants can review the claims and disclosure to determine the scope of the invention and can set forth a group of compounds or diseases which are so similar within the same inventive concept and reduction to practice. Markush claims must be provided with support in the disclosure for each member of the Markush group. See MPEP §608.01(p). Applicant should exercise caution in making a selection of a single member for each substituent group on the base molecule to be consistent with the written description.

Rationale Establishing Patentable Distinctiveness Within Each Group

The above Groups represent general areas wherein the inventions are independent and distinct, each from the other, because of the following reason: **Groups I** and **II** are separate and distinct inventions, because **Group I** claims a process of making a compound of Formula (II), while **Group II** claims methods of uses for a *different* compound [Formula (I)].

Group II listed above is directed to or involves the use of compounds which are recognized in the art as being distinct from one another because of their diverse chemical structure, their different chemical properties, modes of action, different effects and reactive conditions (MPEP §806.04, MPEP §808.01). Additionally, the level of skill in the art is not such that one invention would be obvious over the other invention (Group); i.e., they are patentable over each other. Chemical structures which are similar are presumed to function similarly, whereas chemical structures that are not similar are not presumed to function similarly. The presumption even for similar chemical structures though is not irrebuttable, but may be overcome by scientific reasoning or evidence showing that the structure of the prior art would not have been expected to function as the structure of the claimed invention. Note that in

accordance with the holding of Application of Papesch, 50 CCPA 1084, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) and In re Lalu, 223 USPQ 1257 (Fed. Cir. 1984), chemical structures are patentably distinct where the structures are either not structurally similar, or the prior art fails to suggest a function of a claimed compound would have been expected from a similar structure.

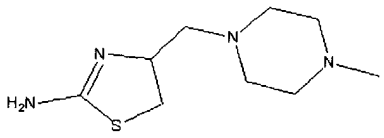
Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In addition, because the potential values for variable "X" in the claims would yield compounds which would be classified in multiple classes and subclasses, a serious burden is imposed upon the examiner to perform a complete search of the defined areas. Therefore, for the reasons given above, the restriction set forth is proper, and not to restrict would impose a serious burden in the examination of this application.

Applicant is advised that the reply to this requirement must include an election of the Invention to be examined even though the requirement be traversed. 37 C.F.R. §1.143.

Applicant is further advised that a reply to this requirement must include an identification of the specific compound that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

During a telephone conversation with James Bolczak, Esq., on November 10, 2004, a provisional election of **Group II** was made, without traverse, and an election of **Parkinson's Disease** and election of the compound of **Formula (I) in Claim 4, namely: 4-(4-methyl-**



piperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine,

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2, and its dependent claims, **Claims 3 – 8,** are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 2 begins by reciting "A method of treating an illness, which involves an abnormal production of nitric oxide (NO) by induction of an inducible NO-synthase (NOS-2), comprising administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula (I) …"

The applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." MPEP

§2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Applying this rule to **Claim 2**, and to its dependent claims, **Claims 3 - 8**, the scope of diseases claimed would thereby include, as just two varied examples, at least "growth of certain forms of tumors such as for example epitheliomas, adenocarcinomas, or sarcomas ..." (see Specification at page 10, lines 6 and 7), and also "Alzheimer's disease" (Id. at p. 10, line 2). However, the scientific data and information disclosed in the Specification are insufficient to enable one skilled in the art to make and/or use the invention to treat any of the illnesses claimed.

Enablement Analysis of Claim 2 and its dependent claims 3 – 8 ("Wands" factors)

As stated in MPEP §2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

The factors to be considered when determining whether a disclosure meet the enablement requirement of 35 U.S.C. §112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

Applying these eight Wands factors to **Claim 2** and its dependent claims, **Claims 3 - 8**:

(1) The Nature of the Invention

Claim 2 claims "the method of treating an illness, which involves an abnormal production of nitric oxide (NO) by induction of an inducible NO-synthase (NOS-2), comprising administering to a patient in need of such a treatment a therapeutically effective of a compound of formula (I) [described]." It is a claim for "method of use."

Claims 3 and **Claim 4** limit the compounds of Formula (I) used in **Claim 2** to three particular compounds (the species identified in **Claim 4** is the same as the third example in **Claim 3**), but do not limit the type of illnesses for which a method of treatment is claimed.

Claim 5 - **Claim 8** recite a group of illnesses to be treated by the method in **Claim 2** to "multiple sclerosis, cerebral, focal or global ischemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety and epilepsy" [**Claim 5**], "Parkinson's disease" [**Claim 6**], "illness caused by inflammatory components" [**Claim 7**], and "illness caused by the growth of a tumor" [**Claim 8**].

(2) The Breadth of Claims

The text of **Claim 2** does not distinguish among those several illnesses which would fall within its scope. As noted above, the applicable rule is that "Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." MPEP §2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claim 2 may be reasonably read to encompass a potentially boundless range, as neither the claims nor Specification expressly define

a closed set of illnesses or disorders caused by the abnormal production of nitric oxide (NO). On page 9, lines 27-28, the Specification only discloses that compounds of formula (I) are useful for treating disorders associated with an excessive NO production *such as* multiple sclerosis, focal or global cerebral ischemia, etc. [emphasis added], and therefore the language of **Claim 2** would properly be interpreted as open-ended.

The scope of illnesses encompassed by **Claim 2** therefore cover such a broad spectrum of human morbidity [comparing the patient populations and/or effects of "Alzheimer's disease" (p. 10, line 2) with, say, "focal or global cerebral ischemia" (p. 9, line 28), "spinal trauma" (p. 10, line 1), "growth of certain forms of tumors" (p. 10, line 6), or even "migraine" (p. 10, line 2)], that it is unreasonable to believe that a method comprised of administering an "effective amount" of any compound could treat *all* of these illnesses or disorders; an unreasonable belief, at least, in the absence of sufficient supporting data in the disclosure.

As another example, **Claim 7,** given its broadest reasonable interpretation in light of the Specification, would also encompass a vast range of illnesses, as neither the Specification nor the claim language defines a closed set of illnesses "caused by inflammatory components" to be treated by the method of Claim 2. The Specification notes only that, "aside from the central nervous system, the induction of NOS-2 is involved in *many pathologies with inflammatory components, such as, for example*, diabetes, atherosclerosis, myocarditis, arthritis, arthrosis, asthma, inflammatory bowel disease, Crohn's disease, peritonitis, gastroesophageal reflux, uveitis, Guillain-Barre syndrome, glomerulo-nephritis, lupus erythromatosus and psoriasis." [emphasis added]. The list of diseases in **Claim 7** is therefore also properly interpreted as open-ended.

Therefore, **Claim 2**, and each of its dependent claims (**Claims 3 – 8**), encompass such a large range of illnesses that the disclosure does not enable a person of ordinary skill in the art to use the "method of treating" described in the claims.

(3) The State of the Prior Art

As noted above, **Claim 2** encompasses methods of treatment of such widely-varied illnesses as the growth of certain forms of tumors (see Specification at p. 10, line 6) and Alzheimer's disease (Id. at p. 10, line 2). However, the state of the art at the time of this application was that methods of treating Alzheimer's disease with therapeutic agents was not well-defined. There are at this time only four medications approved in the United States for the treatment of mild-to-moderate Alzheimer's disease (tacrine, donepezil, rivastigmine, and galantamine), and one medication for moderate-to-severe Alzheimer's disease (memantine). See, e.g., Cummings, Jeffrey, "Alzheimer's Disease," N.Engl.J.Med., 351:56-67 (July 1, 2004) at pp. 58-60; see also Bullock, Roger, "Future directions in the treatment of Alzheimer's disease," Expert Opin. Invest. Drugs 13(4): 303-314 (2004) at pp. 306-309 (discussing uses of chelating agents, anti-inflammatory drugs, immunization, modulation of tau metabolism, etc. as treatments). At the time of this application, however, there do not appear to have been any published clinical studies demonstrating that compounds which are "inhibitors of NO-synthase of Type 2 (NOS-2)" [as in this case] were effective in treating patients with Alzheimer's disease.

Similarly, at the time of this application, the role of nitric oxide (NO) in tumor biology was incompletely understood, and both the promotion and inhibition of NO had been described in treatment of tumor progression. See, e.g., Lala, P.K. and Orucevic, A., "Role of Nitric Oxide in tumor progression: lessons from experimental tumors," Cancer and Metastasis Reviews,

17(1): 91-106 (1998), at Abstract, p. 91, line 2, and p. 102, 2nd col., and p. 103, 1st column (reviewing the roles of NO production in tumor cells and host cells). However, as before, the Specification does not disclose any clinical studies that compounds which are "inhibitors of NO-synthase" would be therapeutic for patients with illnesses caused by tumor growth.

(4) The Relative Skill of Those in the Art

With such a broad range of illnesses and disorders encompassed by **Claim 2**, the skill level of those in the art could vary widely, depending on the disease or disorder. As a general matter, though, practitioners in this art (medical clinicians, pharmacists and/or pharmaceutical chemists) would presumably be highly skilled in the art.

(5) The Predictability or Unpredictability of the Art

A brief survey of scientific literature indicates that the mechanisms of diseases or disorders involving nitric oxide (NO) was not completely understood or settled at the time of the application. As a result, the art has few benchmarks and remains unpredictable, particularly as to methods of using compounds affecting NO-production pathways to treat diseases.

To use another example cited in the Specification, methods for [pharmaceutical] treatment of Alzheimer's disease (listed among illnesses involving the NO-production pathway in the Specification at p. 10, line 2) were unpredictable at the time of this application. While there has been increasing consensus in the field in the intervening years that production of β-amyloid peptide is central to the pathogenesis of Alzheimer's disease, a recent review article stated that not even all proposed treatment regimens targeting the "amyloid cascade" have proven to be effective treatments for Alzheimer's disease. See Cummings, Jeffrey, "Alzheimer's Disease," N.Engl.J.Med., 351:56-67 (July 1, 2004) at p. 61, 1st column.

There are presently only four medications approved in the United States for the treatment of mild-to-moderate Alzheimer's disease (tacrine, donepezil, rivastigmine, and galantamine), and one medication for moderate-to-severe Alzheimer's disease (memantine). Id. at p. 58-60. However, there do not appear to have been any reported clinical studies at the time of this application showing that compounds which are "inhibitors of NO-synthase of Type 2 (NOS-2)" were effective in treating patients with Alzheimer's disease.

In re Fisher, 427 F.2d 833, 839; 166 USPQ 18, 24 (CCPA 1970) held that, "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." In other words, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute.

The nature of the pharmaceutical arts is such that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability, even in view of the high level of skill in the art. This unpredictability is more pronounced where the diseases and disorders disclosed in the Specification are as complex and diverse as multiple sclerosis, Parkinson's disease, Huntington's disease, Alzheimer's disease, migraine, depression, schizophrenia, diabetes, epilepsy, arthritis, asthma, growth of certain forms of tumors, and bacterial infections (See Specification at p. 9. line 25 – p. 10, line 8).

In the review article in the New England Journal of Medicine, *supra*, Dr. Cummings noted that a clinical program to immunize Alzheimer's disease patients with β-amyloid peptide vaccine had to be discontinued when 6% of patients developed encephalitis. See Cummings,

N.Engl.J.Med., vol. 351 at p. 58. Although the vaccine had appeared to reduce pathological signs of Alzheimer's disease in mice, it was ineffective at stimulating removal of β-amyloid deposits from the brain or slowing the rate of cognitive decline in humans. See Robinson, Stephen, et al., "Lessons from the AN 1792 Alzheimer vaccine: lest we forget," Neurobiology of Aging, 25(5): 609-615 (May-June 2004)("[t]he most important lesson to be learned from the AN 1792 trials is that new strategies for treating Alzheimer's Disease should not be tested on humans until they have been extensively tested on non-murine species"); see also Cummings, N.Engl.J.Med. vol., 351 at p. 58. This is evidence that, even where the mechanism of action or *in vitro* activity appears to be favorable, there still remains a high degree of unpredictability when treating patients with Alzheimer's disease.

Consequently, in light of the high level of unpredictability in the art, there is an insufficient disclosure in this application for the treatment or prevention of diseases or disorders as claimed in **Claim 2**.

(6) The Amount of Direction or Guidance Presented

The application provides no additional guidance or direction on the methods to use the compounds of Formula (I) or their pharmaceutical compositions for the method of treatment of diseases or disorders beyond what is disclosed in the language of **Claim 2** ("... comprising administering to a subject in need of such a treatment a therapeutically effective amount of a compound of formula (I)...").

The experimental data disclosed in the Specification provided only that compounds of Formula (I) were tested *in vitro* with NOS-2 and NOS-3 taken from extracts of tissue taken from rats and mice or a recombinant bovine source such the compounds demonstrated to have IC_{50}

values in NOS-2 tests of "less than or equal to 10 μM," and selectivity measured (as a ratio of IC_{50} values for NOS-3/NOS-2) to be "greater than 45." See Specification at p. 10, line 9 – p. 11, line 4. The Specification also discloses that "the compounds are of low toxicity ... their LD_{50} is greater than 40 mg/kg via cutaneous route in mice." Specification at p. 11, lines 5-6.

The disclosure therefore provides very little direction or guidance to enable one of ordinary skill in the art to use compounds of Formula (I) in human subjects for illnesses or disorders for which inhibitors of excessive NO production are needed.

(7) The Presence or Absence of Working Examples

There were no working examples provided by the inventors in **Claim 2**, or in the Specification, where an inhibitor to excessive nitric oxide (NO) production was administered to human subjects for the treatment of any specified disease or disorder.

(8) The Quantity of Experimentation Necessary

With such a broad array of diseases and disorders potentially regulated by nitric oxide pathways, the unpredictability of the art (described above), and the paucity of *in vitro* data and absence of clinical data disclosed in the claims or Specification, a person of ordinary skill in the art would require an undue quantity of experimentation even to select which diseases or disorders, out of all potential candidates, would benefit (i.e., would be treated) by administration of a compound which was an inhibitor of "abnormal production of nitric oxide (NO)"

In addition, a person in the art would have to determine which of the many claimed compounds and compositions would be useful to treat or prevent each disease.

Conclusion of 35 U.S.C. 112, 1st (Enablement) Analysis

MPEP 2164.01(a), 4th paragraph, provides that, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1157, 1562; 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005 (CA FC), states that, "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable," citing Brenner v. Manson, 383 U.S. 519, 536 (1966)(stating, in the context of the utility requirement, that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion"). The Genentech decision continued, "tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. at 1005.

After applying the Wands factors and analysis to **Claim 2**, in light of the applicant's entire disclosure, and in light of the In re Wright, In re Fisher and Genentech opinions discussed above, it is concluded that practice of the claimed invention of **Claim 2** by a person of skill in the art would require undue experimentation to test which diseases can be treated, with no assurance of success.

Therefore, **Claim 2** and its dependent claims, **Claims 3 – 8**, are rejected under 35 U.S.C. §112, 1st paragraph, for failing to disclose sufficient information to enable a person of ordinary skill in the art to "treat an illness which involves abnormal production of nitric oxide (NO) …" by "administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula (I)."

The foregoing rejection under 35 U.S.C. §112, 1st paragraph, can be overcome by identifying (by name) a specific disease or disorder for which there is supporting data disclosed in the Specification for a "method of treating."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Anthony J. Paviglianiti** whose telephone number is **(571) 272-3107**. The examiner can normally be reached on Monday-Friday, 8:30 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane, may be reached at (571) 272-0699.

The FAX phone number for the organization where this application or proceeding is assigned is (571) 273-8300. **This is a new central FAX number for official correspondence.**

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anthony J. Pavigliamti
Patent Examiner
TC-1600, Art Unit 1626

Joseph K. McKane
Supervisory Patent Examiner
TC-1600, Art Unit 1626